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Original Research Article

Incidence of infections in patients with pemphigus vulgaris

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ABSTRACT

Background: Pemphigus is a rare, chronic autoimmune blistering disease of skin and mucous membranes. Autoimmune process and immunosuppressive therapy of pemphigus vulgaris would predispose the patients to infections. Therefore, the objective of this study was to isolate and identify the pathogens in admitted patients suffering from pemphigus vulgaris.
Methods: This was a retrospective observational study based on 68 diagnosed cases of pemphigus vulgaris (PV) admitted during January 1999 to April 2018 in SRN hospital, MLN medical college Prayagraj. Patients who had PV and required admission owing to development of severe symptoms were included while patients with mild symptoms were excluded from the study. These admitted patients, along with routine and radiological examination, were also examined for microbiological examinations of sputum, throat swab, blood, body fluids, skin scrapings, stool and urine when necessary.
Results: Out of the 68 patients, 66.17% patients developed bacterial infections while 33.83% developed fungal infections. The prevalence of bacterial and fungal pathogens in urinary tract is 72.42% and 27.58%, pneumonitis is 29.42% and 70.58%, septicaemia is 81.82% and 18.18% and skin and soft tissue is 87.50% and 12.50% respectively. In meningitis and pulmonary tuberculosis no traces of fungi were recorded. Mortality was seen in 7.35% patients, which was due to bacterial meningitis, septicaemia and fungal pneumonitis.
Conclusions: The present study clearly states that the occurrence of the disease is uncommon but secondary infections are associated with worse prognosis. Therefore, the best regimen for each type of patients should base on the extent of disease and patient's comorbidities.

Keywords: Infection, Pemphigus vulgaris, Autoimmune, Bacterial, Fungal

INTRODUCTION

PV is considered the most common and most severe type of pemphigus and begins with oral lesions appearing as aphtous ulcers or lesions and subsequently affects the skin, with the onset of vesicles and flaccid blisters containing clear or turbid fluid throughout the tegument. The presence of intraepidermal blisters results in loss of integrity of intercellular fixations caused by acantholysis, which means loss of adhesion between epithelial Malpighi cells. Autoantibodies act in desmosemes leading to loss of intercellular adhesion.[1] In PV, IgG autoantibodies are directed against a group of transmembrane adhesion proteins located in desmosomes and named desmogleins (Dsg), more specifically their subtypes 1 (cutaneo-mucous form) and 3 (mucous form), which leads to acantholysis in the suprabasal spinous layer.[1-3]

PV is an organ-specific autoimmune bullous diseases characterized by loss of cell adhesion (acantholysis) and blister formation.[4,5] These dermatoses are proven to be induced by autoimmune phenomenon.[4-6] Considering this

etiology, immunosuppressive therapies are the main treatments available for these disorders. Infections are important complications in these patients attributable to disruption of the epidermal barrier due to the disease itself and immunosuppression induced by treatment.[7,8] Therefore, the objective of this study was to isolate and identify the pathogens in admitted patients suffering from PV.

METHODS

This study was conducted in SRN hospital, MLN medical college Prayagraj. It was a retrospective observational study based on 68 diagnosed cases of PV admitted during January 1999 to April 2018. Only those patients were included who had PV and required admission owing to development of severe symptoms of the disease. While patients with mild symptoms and other form of disease were excluded from the study. After obtaining ethical committee clearance and informed consent, clinical data and laboratory investigations were recorded.

Despite the severity of pemphigus, 34 (50.00%) patients were treated with the combination of 2 mg/kg/day prednisolone and 2.5 mg/kg/day azathioprine. Eleven (16.18%) patients who responded well to azathioprine adjuvant therapy were treated with 2 mg/kg/day prednisolone alone and 23 (33.82%) were treated with 2 mg/kg/day prednisolone and 2 g/day (4×500 mg/day tablet) mycophenolate mofetil.

These patients, along with routine and radiological examination, were also examined for microscopy and cultures of sputum, throat swab, blood, body fluids, skin scrapings, stool and urine when necessary. For bacterial and fungal isolation each specimen was divided into two parts; one was taken for direct routine and microscopic examination and second was inoculated on Columbia blood agar (Biomeurix, France), deoxycholate citrate agar (M065), xylose lysine agar (M031) and sabouraud cycloheximide chloramphenicol agar (M664, Himedia Laboratories Pvt. Ltd., Mumbai, India) for 24 hours incubation at 37ºC. The identification of individual bacteria and yeast were done by Vitek-2 (Biomeurix, France), while identification of individual fungi was based on standard methods such as microscopy, morphology, colony characterization, pigment production and rate of growth.[9]

Ultrasound of the abdomen was performed in all the cases with urinary tract infection (UTI) and the presence of any three of the following criteria's were taken as evidence of tuberculosis (TB): (1) history of cough, fever or a family history of exposure to a case of TB; (2) clinical sign of non-resolving pneumonitis and/or matted lymphadenopathy; (3) a positive chest X-ray (mediastinal lymphadenopathy or non-resolving pneumonitis) or lymph node FNAB findings with acid fast bacilli (AFB); (4) a positive ZN stain; (5) significant ADA levels; (6) Hain positivity for AFB; (7) positive mycobacterium culture.

For the laboratory diagnosis of TB, fluids and aspirates were divided into 4 parts in which 200 µl was taken for routine and cell count 10 µl for estimation of ADA, 500 µl for PCR and 1000 µl was left for ZN stain, and culture. Out of 1000 µl, 900 µl was inoculated in MP bottle for isolation of *Mycobacterium*. This inoculated MP bottle was further incubated in BactAlert 3D system following standard protocols. PCR was done by Hain (line probe method recommended by WHO) in the lab. ADA activity was estimated by turbidometery and was expressed as U/l. Cut off reference range of 10 U/l was taken as positive. Sputum, endotracheal aspirates and pus were decontaminated first and then processed for ZN stain, culture and Hain.[10]

Data were expressed as mean±standard deviation. Statistical significance was defined at a p value of 0.05 by using IBM SPSS 24 version.

RESULTS

During the period January 1999 and April 2018, 68 clinically diagnosed cases of PV were admitted in different hospitals of Allahabad. Out of the 68 patients, 45 (66.17%) patients developed bacterial infections while 23 (33.83%) developed fungal infections. The demographic and base line data of 68 patients are described in Table 1.

Table 1: Demographic and base line data of 68 patients.

S. no.	Demographic and base line data of 68 patients (%)	
1.	Age	58.29±8.845
2.	Sex	88.0 (male), 12.0 (female)
3.	Hospital stay	32.3
4.	Diabetes	52.3
5.	Glomerulonephritis	32.3
6.	Hypertension	13.9
7.	Others	1.5

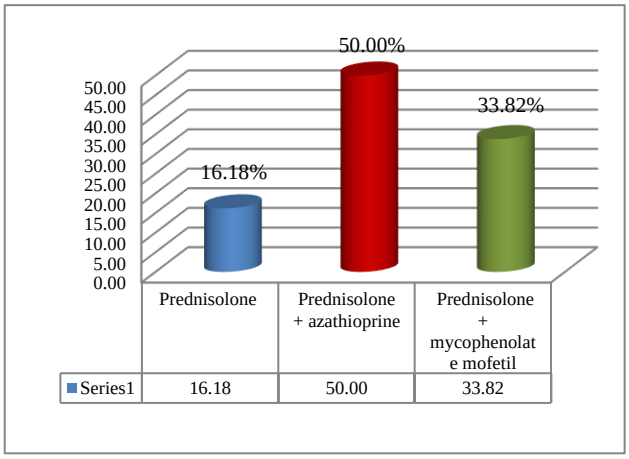
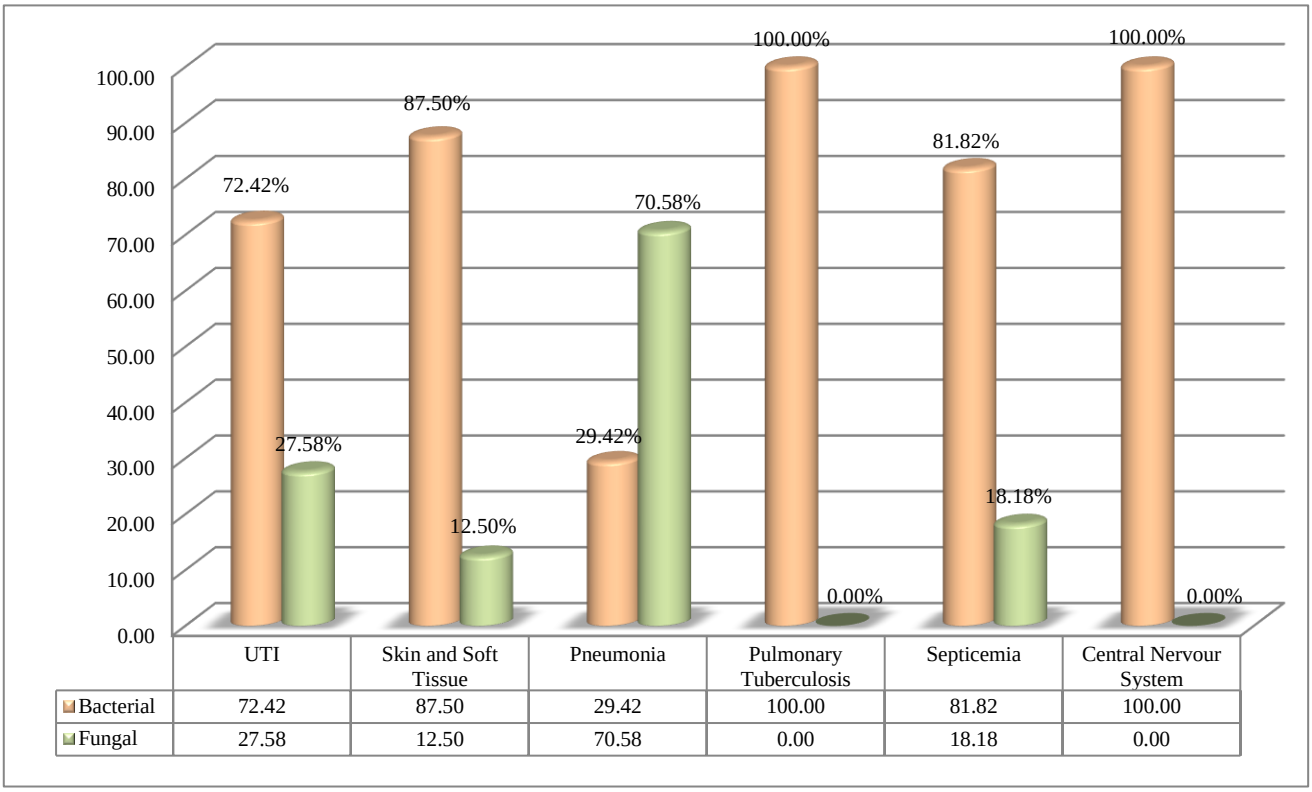


Figure 1: Frequency of infections in patients treated with prednisolone and different combinations.



	UTI	Skin and Soft Tissue	Pneumonia	Pulmonary Tuberculosis	Septicemia	Central Nervour System
Bacterial	72.42	87.50	29.42	100.00	81.82	100.00
Fungal	27.58	12.50	70.58	0.00	18.18	0.00

Figure 2: Incidence of bacterial and fungal pathogens in different infections.

Out of the 68 cases, the mean age of patients with infections was 58.29±8.845 years with males being about 88.0% and females about 12.0%. Frequency of infections in patients treated with prednisolone, prednisolone and azathioprine and prednisolone and mycophenolate mofetil was 16.18%, 50.00% and 33.82% respectively. Highest infection was observed when patient was on prednisolone azathioprine combination as shown in Figure 1. Incidence of bacterial and fungal pathogens in various infections is depicted in Figure 2. Mortality was seen in 5 (7.35%) patients in whom two were suffering with bacterial meningitis, two with fungal septicaemia and one patient with fungal pneumonitis.

DISCUSSION

PV is a well-known autoimmune disease.[11] Nowadays, the relationship between autoimmunity, immunodeficiency and infection is well recognized. It was believed that autoimmunity and immunodeficiency were not separate entities, but rather some connection existed between them.[12,13] On the other hand, hospitalization in addition to immunosuppressive therapy would predispose the PV patients to infection. The average incidence rate of pemphigus in Taiwan during the 8-year study period was 4.714 however, in our study we found 3.57% incidence during 19 years. Patients' distribution according to age and gender differed from country to country. Some reports indicated predominance of females among PV patients and of males among pamphigus foliaceus patients.[15-18] However, in our study incidence of male (88%) was higher than females (12%). In a study, the rate of infection in PV patients with diabetes was significantly higher than in nondiabetics (p=0.044).[19] Belgnaoui et al also reported more severe bacterial infection in diabetics PV patients.[20] Similar results were also observed in our study. We also recorded higher incidence of PV in diabetic patients (52.3%).

In the present study the prevalence of bacterial and fungal infections in urinary tract was 72.42% and 27.58%, pneumonitis was 29.42% and 70.58%, septicaemia was 81.82% and 18.18% and skin and soft tissue was 87.50% and 12.50% respectively. In meningitis and pulmonary tuberculosis no traces of fungi were recorded. In our study we recorded 7.35% mortality in our patients. Ljubojevic et al documented a mortality rate of 8.8% during hospital treatment the main causes of death were cardiopulmonary failure and sepsis.[21] Uzun et al revealed that 4.8% of patients died in a mean follow up period of 25 months, most commonly due to septicaemia.[22] In the study by Kanwar et al among the causes of 10 deaths of PV, sepsis was the most common cause and the responsible pathogenic agent in 4 cases was *Staphylococcus aureus*.[19]

Although previous hospital based research had shown a higher risk of death among patients with pemphigus, little was known about mortality from pemphigus in a large representative COHORT compared with the general population of the same age and gender. Langan et al found that the age and gender-adjusted mortality rate among 138 patients with PV was three times higher than that of

controls.[23] However, underlying causes of death were not examined in that study. We observed causes of mortality were bacterial meningitis, septicaemia and fungal pneumonitis.

Limitations

Data size was relatively small though disease was uncommon. More work should be done to standardize of therapy to reduce the morbidity.

CONCLUSION

The study concludes that the occurrence of the disease is rare but secondary infections are associated with worse prognosis. Therefore, the choice for the best regimen for each type of patients should based on the extent of disease and patient's comorbidities.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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